UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,440	08/16/2001	Henry M. Smilowitz	UCON/187/US	3272

2543 7590 03/09/2004

ALIX YALE & RISTAS LLP
750 MAIN STREET
SUITE 1400
HARTFORD, CT 06103

EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,440	SMILOWITZ ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *7,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the election requirement received on 12/4/03 has been entered. Claims 1-15 are pending in the instant application. Applicant's election without traverse of boron neutron-capture therapy (BNCT) as the species of radiation therapy and excised cells genetically modified to express GM-CSF as the species of genetically altered cells is acknowledged. Although the applicant states that all claims are readable on the elected species, this is incorrect. Claims 7, 14, and 15 are limited to the use of LINAC radiation. Since the applicant has elected boron neutron-capture therapy, claims 7, 14, and 15 are withdrawn from prosecution as being directed to subject matter non-elected without traverse in the instant application. Claims 1-6, and 8-13 are currently under examination. An action on the merits follows.

Please note that claims 1-6 and 8-13 are generic and not limited to the elected species of BNCT and GM-CSF. Since these generic claims have not been found to be allowable, the claims have only been examined to the extent that they read on the elected species.

Priority

This application is a continuation-in-part application of earlier filed application 09/334,312. The applicant has elected excised cells genetically modified to express GM-CSF for examination in the instant application. Neither of the parent applications 60/089,597 or

09/334,312 disclose this embodiment of the invention. The parental applications generally teach genetically modifying cells or excised cells but do not specifically suggest or disclose modifying the cells to express GM-CSF. Therefore, neither of the parent applications support the elected subject matter currently under examination. The applicant is reminded that in order for a later-filed application to receive benefit of priority to an earlier filed application, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). Therefore, the elected subject matter is denied the benefit of priority to parent applications 60/089,597 and 09/334,312. For examination purposes, the effective filing date is therefore the filing date of the instant application, 8/16/01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 depend on claims 1 and are therefore confusing as they recite that the altered cells are "for use in", or "are suitable for injection in" step (c). Step (c) in claim 1, however, recites the administration of radiation therapy. Step **(d)** recites the introduction of altered cells. Thus, the claims are indefinite. The applicant can overcome this rejection by amending claims 8 and 9 to refer to step (d) instead of step (c).

Claim 12 is indefinite in that the metes and bounds of the phrase "a few days" cannot be determined. It is unclear whether a "few" days refers to 3 days, a week, or even longer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatanaka et al. (1978) Acta Neurochirurgica, Vol. 42, 57-72 in view of U.S. Patent No. 5,484,596 (1996), hereafter referred to as Hanna et al., and Dranoff et al. (1993) PNAS, Vol. 90, 3539-3543. The applicant claims methods of treating a malignant solid glioma comprising surgically excising cells of the solid glioma and genetically modifying the cells to express GM-CSF, subjecting the solid glioma to boron neutron-capture therapy (BNCT), and reintroducing the GM-CSF cells to the animal using multiple sequenced injections. The applicant further claims said methods wherein the mass of solid glioma has been previously reduced by surgical and/or radiotherapeutic techniques, or wherein the excised cells are lethally irradiated *in vitro*, or wherein the cells are mixed with an adjuvant.

Hatanaka et al. teaches multi-modality therapy of tumors, particularly tumors of the central nervous system, comprising the combination of radiotherapy and immunotherapy. Specifically, Hatanaka et al. teaches that, "... a surgical and/or radiological measure (and perhaps chemotherapeutic, if immunological suppression can be eliminated), to reduce the number of residual tumour cells in the host's body is an essential prerequisite for tumour immunotherapy" (Hatanaka et al., page 59, first paragraph). With this in mind, Hatanaka et al. recommends the following tumour treatment: reduction of tumor cells by surgery, radiation, or chemotherapy followed by enhancement of immune factors including active immunization with modified tumor cells (Hatanaka et al., page 58, Table 1). In particular, Hatanaka et al. teaches the reduction of tumor cells by enucleation of the tumour followed by boron neutron-capture radiation therapy (Hatanaka et al., page 63, Table 4). Hatanaka et al. also discloses using the

BNCT protocol in glioblastoma patients who were previously treated with radiotherapy, surgery, and chemotherapy (Hatanaka et al, page 70-71).

While Hatanaka et al. does teach the combination of BCNT therapy and active immunization using modified tumour cells, Hatanaka et al. differs from the instant invention by failing to particularly teach the excision and re-introduction of the patient's own tumour cells as the method of active immunization. Hanna et al. supplements Hatanaka et al. by teaching methods of treating resectable solid tumors by surgically removing the solid tumor tissue, preparing an autologous irradiated tumor cell vaccine, and injecting the tumor cells into the patient in multiple sequenced injections, wherein at least several of the tumor cell doses includes the immunogenic adjuvant BCG (Hanna et al., columns 27-28, claims 1-9). Based on the motivation to combine active immunization with BNCT therapy as taught by Hatanaka et al., it would have been *prima facie* obvious to use the autologous tumor vaccine taught by Hanna et al. in the multi-modality tumour therapies taught by Hanna et al. Further, based on the individual success of BNCT therapy as taught by Hatanaka et al. and the success of autologous tumor vaccine therapy taught by Hanna et al. in treating solid tumors, the skilled artisan would have had a reasonable expectation of success in treating a solid glioma by administering BNCT followed by autologous tumor cell immunotherapy.

Although Hatanaka et al. teaches active immunization using modified tumor cells and Hanna et al. teaches autologous tumor vaccines, neither reference teaches genetically modifying the tumor cells to express GM-CSF. Dranoff et al. supplements Hatanaka et al. and Hanna et al. by teaching the treatment of solid tumors by administering irradiated tumor cells which have been transduced with a nucleic acid encoding GM-CSF and which express GM-CSF (Dranoff et

al., page 3540, and page 3542, Figure 4). Dranoff et al. further supplies motivation for using irradiated tumor cells transduced with GM-CSF over non-transduced tumor cells for active immunization by demonstrating that the expression of GM-CSF in several different irradiated tumor types substantially increases anti-tumor immune responses and improves survival in hosts with solid tumors (Dranoff et al., pages 3541 and 3542, Figures 2, 3, and 4). Thus, based on the advantages to using GM-CSF transduced tumor cells over non-transduced tumor cells taught by Dranoff et al., it would have been *prima facie* obvious at the time of filing to genetically modify the autologous tumor cells taught by Hanna et al. with a nucleic acid encoding GM-CSF in order to increase anti-tumor immune responses following immunization. Further, based on the success in increasing anti-tumor immune responses using GM-CSF transduced tumor cell vaccines taught by Dranoff et al., the success of autologous tumor vaccine therapy taught by Hanna et al. in treating solid tumors, and the success of BNCT therapy in treating solid tumors as taught by Hatanaka et al., and the skilled artisan would have had a reasonable expectation of success in treating a solid glioma by administering BNCT followed by autologous tumor cells transduced with GM-CSF.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the

technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER